AF/GP 1638

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BEFORE THE BOARD OF APPEALS AND INTERFERENCES
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Terry et al.	Group Art Unit: 1638
Serial No. 09/365,349	Examiner: Ibrahim, M.
Filed: July 30, 1999	
For: *Heavy Metal Phytoremediation*	Attorney Docket No. B99-085

CERTIFICATE OF MAILING
I hereby certify that this corr is being deposited with the US Postal Service as First Class Mail in an envelope addressed to the Comm of Patents, Washington, D.C. 20231 on January 19, 2001

Signed _____
Richard Osman

SUPPLEMENTAL BRIEF ON APPEAL

The Commissioner of Patents
Washington, D.C. 20231

Dear Commissioner:

This is an appeal from the 10/24/00 rejection of claims 1-24. This is our second appeal of the same claims in this application. The Examiner initially offered rejections under 35UCS112, second paragraph, 35USC102(a) and 35UCS103(a). We avoided the 35UCS112, second paragraph rejections by amendment and appealed the 35USC102(a) and 35USC103(a) rejections. In response to our appeal, the Examiner withdrew the 102(a) and 103(a) rejections. However, instead of allowing these claims, the Examiner now offers new rejections under 35USC112, first paragraph. We likewise appeal these new rejections.

REAL PARTY IN INTEREST

The real party in interest is the Regents of the University of California, the assignee of this patent application.

RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any related appeals or interferences.

STATUS OF THE CLAIMS

Claims 1-24 are pending and subject to this appeal.

STATUS OF THE AMENDMENTS

All Amendments are believed to be properly before the Board.

Prior to issuing the 10/24/00 Action reopening prosecution, the Examiner contacted the undesigned by telephone, proposing that we accept an Examiner's amendment limiting our claims to one particular disclosed type of plant (Brassica), see p.7, line 18 - p.8, line 2 of 10/24/00 Action. This proposal was made with the threat of reopening prosecution on new issues if we declined her amendment. We declined her amendment and she duly carried out her threat to reopen prosecution, *not only on the plant issue*, but also now objecting to every single element of the claim, now alleging that we enable (and describe) no more than a single, particularly disclosed example (10/24/00 Action, p.3, lines 12-16; p.7, lines 1-4). While we submit this supplemental brief in response to the Action as required, we complain that the Office's posture and practice is inconsistent with its applicable law (see 35USC131, 35USC132, 35USC134, 37CFR1.104(b), and MPEP707.07(g)) and its stated purpose. It is not the Examiner's job to see what she can extract or extort from patent applicants. This is not supposed to be like plea-bargaining where the threat of expensive, protracted prosecution is itself offered as an inducement to settle. The Examiner is supposed to be working to assist applicants in securing the best possible patent.

SUMMARY OF THE INVENTION

Heavy metals and metalloids such as cadmium, lead and mercury are an increasing environmental problem worldwide. Green plants can be used to remove heavy metals by sequestrating, stabilizing or biochemically transforming them. This cost-effective and environment-friendly technology is called phytoremediation. Hyperaccumulators - heavy metal accumulating flora collected from metal-contaminated sites - offer one option for the phytoremediation of metal-contaminated sites. However, these hyperaccumulators tend to grow slowly and produce little biomass. An alternative approach is to genetically engineer fast-

growing species to improve their metal tolerance and metal accumulating capacity. (Specification, p.1, lines 12-20).

By overexpressing glutamyl-cysteine synthetase, we have successfully developed transgenic plants that have an increased ability for heavy metal accumulation and tolerance. These plants greatly enhance the efficiency of heavy metal phytoextraction from polluted soils and wastewater. (Specification, p.3, lines 12-15).

The claims are directed to a plant which is genetically engineered to overexpress glutamylcysteine synthetase and thereby provides enhanced heavy metal accumulation as compared with a corresponding wild type plant. In particular embodiments, the plant comprises a gene encoding the glutamylcysteine synthetase operably linked to a heterologous promoter and is a member of the brassicaceae family, such as *Brassica juncea*. Applicable heavy metals include chromium, molybdenum, tungsten, cadmium, mercury and uranium. In more particular embodiments, the enhanced accumulation is at least 50% greater than an otherwise comparable untransformed plant and/or the plant grows not significantly differently than a corresponding wild type plant under non-heavy metal conditions. See specification, p.3, lines 18-23 and pending claims.

The pending method claims provide for decreasing heavy metal content of a medium (such as soil), comprising the steps of: (a) identifying a medium as containing an excessive amount of a heavy metal; and (b) growing a subject plant in the medium, under conditions wherein the glutamylcysteine synthetase is overexpressed, whereby the plant provides enhanced accumulation of the heavy metal, whereby the heavy metal content of the medium is decreased. See specification, p.3, lines 23-26 and pending claims.

ISSUE

I. WHETHER CLAIMS 1-24 ARE PATENTABLE UNDER 35USC112, first paragraph.

GROUPING OF THE CLAIMS

Claims 1, 2, 8, 13, 15, 20, 22 shall be considered together as a group; claim 3 shall be considered separately; claims 4, 21 shall be considered as a group; claims 5, 7, 14 shall be

considered as a group; claim 6 shall be considered separately; claim 19 shall be considered separately; claims 9, 11, 12, 16, 18, 23 shall be considered as a group; claim 10, 17, 24 shall be considered as a group.

ARGUMENT

I. CLAIMS 1-30 ARE PATENTABLE UNDER 35USC112, first paragraph.

(a) Enablement

(i) Claims 1, 2, 8, 13, 15, 20 and 22.

The enablement issue is whether the specification enables one of ordinary skill in the art to practice the invention as claimed without undue experimentation. Here, the product claims are drawn to a plant which is genetically engineered to overexpress glutamylcysteine synthetase and thereby provides enhanced heavy metal accumulation as compared with a corresponding wild type plant. The corresponding method claims require only two steps (a) identifying a medium as containing an excessive amount of a heavy metal; and (b) growing a subject plant in the medium, under conditions wherein the glutamylcysteine synthetase is overexpressed, whereby the plant provides enhanced accumulation of the heavy metal, whereby the heavy metal content of the medium is decreased. The specification teaches, describes and exemplifies the claimed plant and every element of the method, including the selected plant, heavy metal contaminant, medium and glutamylcysteine synthetase, readily enabling one of ordinary skill in the art to practice the two steps without undue experimentation.

The specification teaches that "a wide variety of plants may be used, as urged by the particular trace element, medium, site geology, topology, weather, etc. Additional factors for selection include large biomass production, relatively high trace element accumulation capacity, and ease of genetic engineerability", citing Zhu et al., 1999, Plant Physiol 119:73-79. Specification, p.4, lines 6-9. The claims do not encompass "any plant" as repeatedly alleged by the Examiner, but rather only a plant structurally limited to a plant genetically engineered to overexpress glutamylcysteine synthetase and functionally limited to one which does in fact overexpress the recited glutamylcysteine synthetase *and* thereby provides enhanced accumulation of the targeted heavy metal as compared with a corresponding wild type plant (see claim 1).

"Suitable plants are readily screened for requisite engineerability and expression from examplars of candidate plant varieties by those skilled in the art of plant genetic engineering, as exemplified below." Specification, p.4, lines 9-11. The specification offers a large number of suitable, commercially available varieties of exemplary plant source materials (p.4, line 11 - p.6, line 9). Furthermore, the specification describes diverse exemplary plant species demonstrating enhanced elemental assimilation in wild-type plants and the corresponding plant overexpressing a variety of recombinant glutamylcysteine synthetase genes (p.7, line 26 - p.8, line 18); exemplified plants include Brassica juncea, Populus angustifolia, Nicotiana tabacum and Silene cucubalis. The suitability of any given plant is readily ascertained by simple substitution into the same method.

The specification teaches that the claimed plants and methods are amenable to accumulating a wide variety of heavy metals, enumerates numerous examples, and provides guidance on selecting preferred species (Specification, p.6, lines 20-27). Furthermore, the specification describes enhanced assimilation of a variety of exemplary heavy metals in diverse plant species expressing a recombinant glutamylcysteine synthetase gene (p.7, lines 14-19); exemplified heavy metals include Cd (cadmium), Mo (molybdenum), W (tungsten), U (uranium) and Hg (mercury). The suitability of any given heavy metal is readily ascertained by simple substitution into the same method, as repeatedly exemplified.

The specification teaches that the claimed methods are applicable to phytoremediation of media such as soil or water (Specification, p.3, line 24). The medium of the claimed methods is structurally limited to a medium containing an excessive amount of a heavy metal and functionally limited to a medium wherein the heavy metal content of the medium is decreased by the subject method. Furthermore, the specification describes phytoremediation from a variety of media by enhanced assimilation of exemplary heavy metals in diverse plant species expressing a recombinant glutamylcysteine synthetase gene (p.8, lines 1-18); exemplified media include hydroponic medium, loamy soil, sandy soil and clay soil. The suitability of an alternative soil or other medium is readily ascertained by simple substitution into the same method, as repeatedly exemplified.

The claims are limited to a glutamylcysteine synthetase gene. The specification specifically teaches the use of glutamylcysteine synthetase genes, describing suitable expression

constructs and alternative promoters (p.6, lines 10-19). Glutamylcysteine synthetase genes are well known, defined reagents and their use is well-established (see, p.3, lines 1-10, noting that ECS is an abbreviation for glutamylcysteine synthetase, see p.2, lines 7-8). Furthermore, the specification offers detailed exemplification of the claimed plants and phytoremediation of media by enhanced assimilation of heavy metals using plant species expressing a variety of alternative glutamylcysteine synthetase genes (p.7, lines 19-22) and under the control of a variety of alternative promoter elements (p.7, lines 23-26).

The Action offers no more than an assortment of false allegations and a gratuitous legal citation without any analysis or explanation as to how it is relevant. The Action asserts "the specification provides guidance only for the transformation of Brassica juncea with the ECS gene from E. Coli driven by (*sic*) double-enhanced 35S CaMV promoter, and wherein the analysis of heavy (*sic*) tolerance involves only (*sic*) in hydroponic or agar medium with Cd concentrations of 0.15-0.25 mM of CdSO4." (10/24/00 Office Action p.3, lines 12-15). Only a failure to read the bulk of the specification could support such an allegation. The Action asserts that "Applicants broadly claim any plant comprising a gene from any source encoding glutamylcysteine synthetase"(10/24/00 Office Action, p.3, lines 6-7), an allegation that ignores both structural and functional limitations of the claims. The Action asserts that "no guidance has been presented for the removal of exemplified or non-exemplified heavy metals from soil" (10/24/00 Action, p.3, lines 17-19) – an allegation that could only be made by ignoring much of the specification, particularly Table 2, p.7, line 10 - p.8, line 18.

The Action cites *In re Wands,* 8USPQ2d1400 (Fed. Cir. 1988), listing factors the Court considered relevant to determining whether or not undue experimentation would be required to practice a claimed invention, but then follows up with only a rambling discussion of the prior art that appears to confuse non-obviousness (unexpected results) with undue experimentation. As we attempted to explain in our Response of Sept 21, 2000, the invention is premised on Applicants' finding that the recited glutamylcysteine synthetase effects heavy metal accumulation, is causative of heavy metal accumulation and is rate-limiting of heavy metal accumulation. The disclosure establishes a predictable relationship between heavy metal exposure and overexpression of glutamylcysteine synthetase; namely, that such overexpression

promotes enhanced accumulation of the metal. This relationship is shown to hold across numerous and diverse exemplary plant species (supra). Accordingly, the specification aptly enables one of ordinary skill in the art to practice the method in any plant which is genetically engineered to overexpress glutamylcysteine synthetase and thereby provide enhanced accumulation of the heavy metal.

The uncertain and unpredictable relationship cited in our initial Appeal Brief (e.g. p.4, line 24) relates not to the subject methods or their extrapolation to various plants, but rather to the prior art establishment of an uncertain and unpredictable relationship between glutamylcysteine synthetase expression and heavy metal exposure. As explained in that Brief, Chen et al. (1994) report that mutant tomato cells selected for cadmium tolerance show increased ECS activity.

A detailed reading of Chen and subsequent work from Chen's laboratory (not cited in the Action) reveals that the prior art not only fails to suggest the claimed invention, but in fact teaches directly away from it. In their discussion section, Chen acknowledges that the relationships between ECS activity, glutathione synthetase (GS) activity, phyotochelatin (PC) synthesis, heavy metal tolerance and heavy metal accumulation are by no means clear. While Chen's results are similar to those of Steffens et al. (1989), cited by Chen on p.238 col 1, lines 50-53, other published reports suggest the opposite. For example, at p.238, col 2, line 20-25 Chen also cites de Knecht et al. (1992) for demonstrating that Cd-tolerant plants can synthesize fewer PCs than sensitive plants exposed to the same Cd concentration. Other data cited by Chen suggest that this mechanism of Cd-tolerance may not provide a practical route for generating useful plants. First, Chen's Cd-tolerance is not stable (Chen, p.238, col 1, lines 12-14) and second, such metal tolerant plants demonstrate poor growth characteristics (Chen, p.238, col 1, lines 22-25). Chen concludes by suggesting that future development of transgenic plants with altered capacities to synthesize either GSH or PCs might be used to test their hypothesis that increased GSH and/or PC synthesis increases Cd tolerance.

The senior author of Chen et al. subsequently reported on exactly these experiments (see our Specification, p.3, lines 5-9 and the Goldsbrough, 1999, reference cited therein) and like Arisi's poplars, Goldsbrough's transformed Arabidopsis plants provided no increase in heavy

metal accumulation compared with controls. Specifically, Goldsbrough reports that while ECS could restore some degree of Cd tolerance to a Cd-sensitive mutant (a *cad2* mutant having reduced GSH levels), this gene did not increase Cd tolerance of wild type plants (Goldsbrough, p.230, line 35)[1]. Interestingly, Goldsbrough also further confounds the teachings of Chen by reporting that the ECS gene does not show any change in RNA expression in plants or cells that are exposed to Cd (Goldsbrough, p.230, lines 28-30).

The prior art does not suggest modifying Raskin to overexpress ECS, rather than metallothioneins, and thereby secure a plant providing enhanced heavy metal accumulation. The prior art establishes an uncertain and unpredictable relationship between ECS expression and heavy metal accumulation, and specifically teaches (in both Noctor et al. and Goldsbrough) that over expression of ECS will not yield heavy metal accumulators.

What these references show is that simple upregulation of a gene (such as ECS) in response to cultivation in the presence of a heavy metal does not suggest that the plant will demostrate enhanced accumulation of the heavy metal. The prior art establishes an uncertain and unpredictable relationship between glutamylcysteine synthetase and heavy metal exposure, and specifically teaches (in Noctor et al., Goldsbrough and Terry) that overexpression of enzymes upregulated upon heavy metal exposure, including glutamylcysteine synthetase, will not yield heavy metal accumulators.

This unpredictability relates to extrapolating from gene upregulation to metal accumulation and has no bearing on substituting one plant for another in the claimed methods, wherein enhanced accumulation is demonstrated – in fact, it is demonstrated in a variety of diverse exemplary plants. The specification aptly enables one of ordinary skill in the art to practice the method in any plant which is genetically engineered to overexpress glutamylcysteine

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[1] The Examiner's Final Action of 10/24/00 suggested that the positive result with the Cd-sensitive mutants supports the rejection. We believe that would only be true if the claims encompassed plants which accumulate normal amounts of heavy metal. However, the present invention and pending claims do not relate to sensitive mutant plants restored by genetic engineering to accumulate normal amounts of heavy metal. The invention relates to hyper-accumulators. The claims expressly recite that enhanced means enhanced over normal, wild-type accumulation - the claims do not encompass a Cd-sensitive mutant engineered to provide merely normal, wild-type heavy metal accumulation.

synthetase and thereby provide enhanced accumulation of the heavy metal.

Finally, however inaptly cited, the lessons of *In re Wands* are instructive. Any experimentation necessary for practicing alternative embodiments of the invention involves only substituting alternative plants, constructs or media in the exemplified protocols, and compares overwhelmingly favorably to that of *In re Wands,* 8USPQ2d1400 (Fed. Cir. 1988). In *Wands*, the Federal Circuit held that making and screening monoclonal antibodies, even back in 1980, did not constitute undue experimentation. Practicing our method with different plants, constructs or media, beyond those many exemplified species, is minor compared with the permitted experimentation under *Wands*. In particular, after immunizing and confirming the presence of specific antibodies, practitioners of Wands' invention are faced with the daunting and unpredictable tasks of surgically removing the animal's spleen; separating lymphocytes therefrom; mixing the lymphocytes with myeloma cells; treating the mixture to cause a few of the lymphocytes to fuse with a few myeloma cells; isolating from the enormous number of cells in the mixture hybridoma cells that secrete the desired antibody through a series of screening procedures. The entire process from immunization to serial cloning takes months. The technical feats involved include aseptic surgery, cell fusions, tissue culture with transformed cells which require special health and environmental safety measures, dilution cloning, usually into a bed of immature thymocytes which again requires further aseptic surgery, radiolabel or enzyme-linked immunoassays of secreted antibody, etc. In fact, the vast majority (>97%) of Wands' efforts to produce the claimed antibodies failed. As the 35USC112-compliant experimentation required to generate and screen monoclonal antibodies per *Wands* is vastly more extensive and unpredictable than that required to practice our phytoremediation method in alternative plants, constructs or media, our claims are in compliance with 35USC112. To the extent the Examiner is concerned that the claims might include inoperable embodiments, "it is not a function of the claims to specifically exclude possible inoperative substances", *In re Dinh-Nguyen*, 181USPQ46,48 (CCPA 1974); see also, *In re Wands* (8 USPQ2d 1400 (Fed Cir 1988), "Even if we were to accept the PTO's 2.8% success rate, we would not be required to reach a conclusion of undue experimentation"; see also, *Atlas Powder Co.*, 224USPQ409,414 (Fed Cir 1994).

(ii) Claim 3 is specifically limited to Brassicaceae plants and hence, avoids the Examiner's (inaccurate) complaint that the claims encompass any plant. Ironically, this is the very limitation the Examiner sought before reopening prosecution.

(iii) Claims 4 and 21 are specifically limited to the *Brassica juncea* plant, which even further avoids the Examiner's (inaccurate) complaint that the claims encompass any plant. This is also the plant species particularly exemplified on p.8, line 21. Ironically, this species limitation is even more restrictive than the Brassicaceae limitation the Examiner offered before reopening prosecution.

(iv) Claims 5, 7 and 14 are limited to specifically enumerated heavy metals, which further avoids the Examiner's (inaccurate) complaint that the claims encompass phytoremediation of "any heavy metal" (10/24/00 Office Action, p.5, lines 3-4). These particularly recited metals are specifically exemplified in Table 2 (Specification, p.7, lines 14-19).

(v) Claim 6 is further limited to the method wherein the heavy metal is cadmium (Cd) or mercury (Hg), which even further avoids the Examiner's (inaccurate) complaint that the claims encompass phytoremediation of "any heavy metal". Not only are these metals subject to exemplification in Table 2 (Specification, p.7, lines 14-19), but Cd in particular is the metal exemplified on p.11, line 19. Hg is the group IIB post-transition element immediately below (one principal quantum number greater than) Cd; accordingly it has the same valence configuration and has been well known for over 100 years to have similar chemical properties.

(vi) Claim 19 is limited to a medium of soil, which further avoids the Examiner's (inaccurate) complaint that the claim is applicable to "any medium". Various suitable soil media are repeatedly exemplified in Table 2 (Specification, p.8, lines 1-18).

(vii) Claims 9, 11, 12, 16, 18 and 23 are limited to both a particular plant species, *Brassica juncea* and a specifically enumerated heavy metal. These claims further avoid *both* the

Examiner's complaint that the claims encompass phytoremediation of "any heavy metal" and her complaint that they encompass any plant.

(viii) Claims 10, 17 and 24 are limited to both a particular plant species, *Brassica juncea* and a specifically enumerated heavy metal, Cd or Hg. These claims even further avoid *both* the Examiner's complaint that the claims encompass phytoremediation of "any heavy metal" and her complaint that they encompass any plant.

(b) Written Description

(i) Claims 1, 2, 8, 13, 15, 20, 22.

The written description issue is whether claimed subject matter was described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Here, the product claims are drawn to a plant which is genetically engineered to overexpress glutamylcysteine synthetase and thereby provides enhanced heavy metal accumulation as compared with a corresponding wild type plant. The corresponding method claims require only two steps (a) identifying a medium as containing an excessive amount of a heavy metal; and (b) growing a subject plant in the medium, under conditions wherein the glutamylcysteine synthetase is overexpressed, whereby the plant provides enhanced accumulation of the heavy metal, whereby the heavy metal content of the medium is decreased. The specification teaches, describes and exemplifies the claimed plant and every element of the method, including the selected plant, heavy metal contaminant, medium and glutamylcysteine synthetase, abundantly demonstrating that the claimed subject matter was described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification teaches that "a wide variety of plants may be used, as urged by the particular trace element, medium, site geology, topology, weather, etc. Additional factors for selection include large biomass production, relatively high trace element accumulation capacity, and ease of genetic engineerability", citing Zhu et al., 1999, Plant Physiol 119:73-79.

Specification, p.4, lines 6-9. The claims do not encompass "any plant" as repeatedly alleged by the Examiner, but rather only a plant structurally limited to a plant genetically engineered to overexpress glutamylcysteine synthetase and functionally limited to one which does in fact overexpress the recited glutamylcysteine synthetase *and* thereby provides enhanced accumulation of the targeted heavy metal as compared with a corresponding wild type plant (see claim 1). "Suitable plants are readily screened for requisite engineerability and expression from examplars of candidate plant varieties by those skilled in the art of plant genetic engineering, as exemplified below." Specification, p.4, lines 9-11. The specification offers a large number of suitable, commercially available varieties of exemplary plant source materials (p.4, line 11 - p.6, line 9). Furthermore, the specification describes diverse exemplary plant species demonstrating enhanced elemental assimilation in wild-type plants and the corresponding plant overexpressing a variety of recombinant glutamylcysteine synthetase genes (p.7, line 26 - p.8, line 18); exemplified plants include Brassica juncea, Populus angustifolia, Nicotiana tabacum and Silene cucubalis.

The specification teaches that the claimed plants and methods are amenable to accumulating a wide variety of heavy metals, enumerates numerous examples, and provides guidance on selecting preferred species (Specification, p.6, lines 20-27). Furthermore, the specification describes enhanced assimilation of a variety of exemplary heavy metals in diverse plant species expressing a recombinant glutamylcysteine synthetase gene (p.7, lines 14-19); exemplified heavy metals include Cd (cadmium), Mo (molybdenum), W (tungsten), U (uranium) and Hg (mecury).

The specification teaches that the claimed methods are applicable to phytoremediation of media such as soil or water (Specification, p.3, line 24). The medium of the claimed methods is structurally limited to a medium containing an excessive amount of a heavy metal and functionally limited to a medium wherein the heavy metal content of the medium is decreased by the subject method. Furthermore, the specification describes phytoremediation from a variety of media by enhanced assimilation of exemplary heavy metals in diverse plant species expressing a recombinant glutamylcysteine synthetase gene (p.8, lines 1-18); exemplified media include hydroponic medium, loamy soil, sandy soil and clay soil.

The claims are limited to a glutamylcysteine synthetase gene. The specification

specifically teaches the use of glutamylcysteine synthetase genes, describing suitable expression constructs and alternative promoters (p.6, lines 10-19). Glutamylcysteine synthetase genes are well known, defined reagents and their use is well-established (see, p.3, lines 1-10, noting that ECS is an abbreviation for glutamylcysteine synthetase, see p.2, lines 7-8). Furthermore, the specification offers detailed exemplification of the claimed plants and phytoremediation of media by enhanced assimilation of heavy metals using plant species expressing a variety of alternative glutamylcysteine synthetase genes (p.7, lines 19-22) and under the control of a variety of alternative promoter elements (p.7, lines 23-26).

The Action here again offers no more than an assortment of false allegations and two gratuitous legal citations, without any analysis or explanation as to how they are relevant. The Action asserts that "claims are broadly drawn to a multitude of plant species overexpressing a multitude of ECS (*sic*) for enhanced accumulation of a multitude of heavy metal (*sic*)" (10/24/00 Office Action, p.5, lines 13-14). In fact, as detailed above, the claimed plants and methods are carefully restricted to structurally and functionally limited plants and methods. The Action asserts that "the specification only provides guidance for the transformation of Brassica juncea to overexpress ECS for Cd tolerance" (10/24/00 Office Action, p.5, lines 16-17), an allegation that could only be made by not reading the specification as abstracted in some detail above.

The Action cites *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016, 1021, 1027, (Fed, Cir. 1991) and *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), and offers a generalized statement of their respective holdings, but without any analysis or explanation as to how they are relevant. Nevertheless, we visit the (ir)relevance of these cases to the present claims.

Though routinely (mis)cited for it, the relevant holdings of *Amgen* concerned not the written description requirement of 35USC112 per se, but rather a priority (conception) claim and an enablement issue. These issues arose with two claims:

> 2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.
>
> 7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property

of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.

As to claim 2, the Court found that at the time of the priority claim, the inventors had not cloned the claimed composition, they had not isolated it, and they did not know its sequence (structure). Based on this abject failure to possess their claimed invention on their claimed priority date, the Court held that "it is not sufficient to define [a claimed gene] solely by its principle biological property, e.g., encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property ... when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated." *Amgen* at p.1021.

As to enablement of claim 7, the Court construed the claim to encompass "all DNA sequences suitable for use in securing expression in a procaryotic or eucaryotic host cell of a polypeptide product having at least a part of the primary structural conformation and one or more of the biological properties of erythropoietin, and selected from among: (a) the DNA sequences set out in FIGS. 5 and 6; (b) DNA sequences which hybridize to the DNA sequences defined in (a) or fragments thereof; and (c) DNA sequences which, but for the degeneracy of the genetic code, would hybridize to the DNA sequences defined in (a) and (b)." *Amgen* at p.1026. Based on this construction and factual findings, the Court concluded: "Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, with attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity." *Amgen* at 1027.

The subject claims present no *Amgen* issue. We are not claiming priority to a disclosure that does not describe the claimed methods and we are not claiming an infinite, unpredictable genus while disclosing only a handful of nonrepresentative species. In contrast, the specification fully describes, teaches and exemplifies the claimed method, including alternative embodiments

of each and every element of the claims.

The Action also cites *University of California v. Eli Lilly and Co.* In *Lilly*, the applicant claimed a genus of every "vertebrate cDNA encoding insulin", while only disclosing the corresponding rat cDNA. Isolating other members of the claimed cDNA genus would involve de novo cloning from each species, as the claim encompasses sequences which are, or are the same as, sequences isolated from a given vertebrate species. The Federal Circuit determined that the rat cDNA did not reasonably convey possession of the genus of every vertebrate cDNA. In essence, the Applicant in *Lilly* instructed the practitioner to go out and clone de novo novel sequences from alternative species.

The subject claims present no *Lilly* issue. We claim no cDNA, nor require the practitioner isolate anything from nature. We teach, describe and exemplify, in multiple embodiments, all the elements of the claimed method. Contemplating and practicing alternative elements involves no more than substituting known reagents, according to described guidelines, into a provided protocol.

Finally, the Action purports to address our remarks filed 10/21/00 by arguing that Goldsbrough, Noctor and de Knecht did not show an increase in "heavy metal tolerance" (10/24/00 Office Action, p.7, lines 8-10). First, these references have all been addressed in our initial Appeal Brief filed 8/1/00 in response to the Examiner's now withdrawn prior art rejections. Second, any failure of the prior art to achieve the claimed invention goes to the unexpectedness of our results, and hence nonobviousness - not the adequacy of our written description which lies in our specification. And, contrary to the false allegations of the Action, our specification does teach how to practice the claimed invention in the recited species and does provide predictable results (see, p.7, line 10 - p.8, line 19). Finally, the Examiner persists in alleging that the claims relate to heavy metal *tolerance* - they do not. The relate to heavy metal *accumulation*, a point which we painstakingly explained in our remarks filed 10/21/00.

(ii) Claim 3 is specifically limited to Brassicaceae plants and hence, avoids the Examiner's (inaccurate) complaint that the claims encompass *any* plant (10/24/00 Office Action, p.6, line 7). Ironically again, this is the very limitation the Examiner sought before reopening prosecution.

(iii) Claims 4 and 21 are specifically limited to the *Brassica juncea* plant, which even further avoids the Examiner's (inaccurate) complaint that the claims encompass *any* plant (10/24/00 Office Action, p.6, line 7). This is also the plant species particularly exemplified on p.8, line 21. Ironically again, this species limitation is even more restrictive than the Brassicaceae limitation the Examiner offered before reopening prosecution.

(iv) Claims 5, 7 and 14 are limited to specifically enumerated heavy metals, which further avoids the Examiner's (inaccurate) complaint that the claims encompass phytoremediation of "any heavy metal" (10/24/00 Office Action, p.5, lines 3-4). These particularly recited metals are specifically exemplified in Table 2 (Specification, p.7, lines 14-19).

(v) Claim 6 is further limited to the method wherein the heavy metal is cadmium (Cd) or mercury (Hg), which even further avoids the Examiner's (inaccurate) complaint that the claims encompass phytoremediation of "any heavy metal". Not only are these metals subject to exemplification in Table 2 (Specification, p.7, lines 14-19), but Cd in particular is the metal exemplified on p.11, line 19. Hg is the group IIB post-transition element immediately below (one principal quantum number greater than) Cd; accordingly it has the same valence configuration and has been well known for over 100 years to have similar chemical properties.

(vi) Claim 19 is limited to a medium of soil, which further avoids the Examiner's (inaccurate) complaint that the claim is applicable to "any medium". Various suitable soil media are repeatedly exemplified in Table 2 (Specification, p.8, lines 1-18).

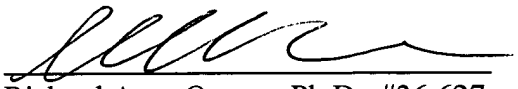
(vii) Claims 9, 11, 12, 16, 18 and 23 are limited to both a particular plant species, *Brassica juncea* and a specifically enumerated heavy metal. These claims further avoid *both* the Examiner's complaint that the claims encompass phytoremediation of "any heavy metal" and her complaint that they encompass any plant.

(viii) Claims 10, 17 and 24 are limited to both a particular plant species, *Brassica juncea* and a specifically enumerated heavy metal, Cd or Hg. These claims even further avoid *both* the Examiner's complaint that the claims encompass phytoremediation of "any heavy metal" and her complaint that they encompass any plant.

The claimed method is amply enabled and described. The pending rejections are facially without merit or support. They also reflect an abuse of administrative process. Applicants respectfully request reversal of the pending Final Action by the Board of Appeals.

Applicants hereby petition for any necessary extension of time pursuant to 37 CFR 1.136(a). The Commissioner is hereby authorized to charge any necessary fees (small entity) or credit any overcharges associated with this communication to our Deposit Account No. 19-0750 (order no.B99-085).

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP



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CLAIMS ON APPEAL

1. A plant which is genetically engineered to overexpress glutamylcysteine synthetase and thereby provides enhanced heavy metal accumulation as compared with a corresponding wild type plant.

2. A plant according to claim 1 comprising a gene encoding the glutamylcysteine synthetase operably linked to a heterologous promoter.

3. A plant according to claim 1 which is a member of the brassicaceae family.

4. A plant according to claim 1 which is a *Brassica juncea.*

5. A plant according to claim 1 wherein the heavy metal is selected from the group consisting of chromium, molybdenum and tungsten.

6. A plant according to claim 1 wherein the heavy metal is selected from the group consisting of cadmium and mercury.

7. A plant according to claim 1 wherein the heavy metal is uranium.

8. A plant according to claim 1, wherein the enhanced accumulation is at least 50% greater than an otherwise comparable untransformed plant.

9. A plant according to claim 1, wherein the plant comprises a gene encoding the glutamylcysteine synthetase operably linked to a heterologous promoter, the plant is a *Brassica juncea*, the heavy metal is selected from the group consisting of chromium, molybdenum and tungsten and the enhanced accumulation is at least 50% greater than an otherwise comparable untransformed plant.

10. A plant according to claim 1, wherein the plant comprises a gene encoding the glutamylcysteine synthetase operably linked to a heterologous promoter, the plant is a *Brassica juncea*, the heavy metal is selected from the group consisting of cadmium and mercury and the enhanced accumulation is at least 50% greater than an otherwise comparable untransformed plant.

11. A plant according to claim 1, wherein the plant comprises a gene encoding the glutamylcysteine synthetase operably linked to a heterologous promoter, the plant is a *Brassica juncea*, the heavy metal is selected from the group consisting of tellurium and polonium and the enhanced accumulation is at least 50% greater than an otherwise comparable untransformed plant.

12. A plant according to claim 1, wherein the plant comprises a gene encoding the glutamylcysteine synthetase operably linked to a heterologous promoter, the plant is a *Brassica juncea*, the heavy metal is uranium and the enhanced accumulation is at least 50% greater than an otherwise comparable untransformed plant.

13. A method for decreasing heavy metal content of a medium, comprising the steps of: (a) identifying a medium as containing an excessive amount of a heavy metal; and (b) growing a plant according to claim 1 in the medium, under conditions wherein the glutamylcysteine synthetase is overexpressed, whereby the plant provides enhanced accumulation of the heavy metal, whereby the heavy metal content of the medium is decreased.

14. A method for decreasing heavy metal content of a medium, comprising the steps of: (a) identifying a medium as containing an excessive amount of a heavy metal; and (b) growing a plant according to claim 7 in the medium, under conditions wherein the glutamylcysteine synthetase is overexpressed, whereby the plant provides enhanced accumulation of the heavy metal, whereby the heavy metal content of the medium is decreased.

15. A method for decreasing heavy metal content of a medium, comprising the steps of: (a) identifying a medium as containing an excessive amount of a heavy metal; and (b) growing a plant according to claim 8 in the medium, under conditions wherein the glutamylcysteine synthetase is overexpressed, whereby the plant provides enhanced accumulation of the heavy metal, whereby the heavy metal content of the medium is decreased.

16. A method for decreasing heavy metal content of a medium, comprising the steps of: (a) identifying a medium as containing an excessive amount of a heavy metal; and (b) growing a plant according to claim 9 in the medium, under conditions wherein the glutamylcysteine synthetase is overexpressed, whereby the plant provides enhanced accumulation of the heavy metal, whereby the heavy metal content of the medium is decreased.

17. A method for decreasing heavy metal content of a medium, comprising the steps of: (a) identifying a medium as containing an excessive amount of a heavy metal; and (b) growing a plant according to claim 10 in the medium, under conditions wherein the glutamylcysteine synthetase is overexpressed, whereby the plant provides enhanced accumulation of the heavy metal, whereby the heavy metal content of the medium is decreased.

18. A method for decreasing heavy metal content of a medium, comprising the steps of: (a) identifying a medium as containing an excessive amount of a heavy metal; and (b) growing a plant according to claim 11 in the medium, under conditions wherein the glutamylcysteine synthetase is overexpressed, whereby the plant provides enhanced accumulation of the heavy metal, whereby the heavy metal content of the medium is decreased.

19. A method according to claim 13, wherein the medium is soil.

20. A plant according to claim 1 wherein the plant grows not significantly differently than a corresponding wild type plant under non-heavy metal conditions.

21. A plant according to claim 4 wherein the plant grows not significantly differently than a corresponding wild type plant under non-heavy metal conditions.

22. A method according to claim 13 wherein the plant grows not significantly differently than a corresponding wild type plant under non-heavy metal conditions.

23. A method according to claim 16 wherein the plant grows not significantly differently than a corresponding wild type plant under non-heavy metal conditions.

24. A method according to claim 17 wherein the plant grows not significantly differently than a corresponding wild type plant under non-heavy metal conditions.